REMARKS

Continued prosecution and consideration of the claimed subject matter in the accompanying patent application is respectfully requested.

Claims 1-25 are cancelled, as are claims 27-30, 33, 35, 42-45, and 47-51. Claims 42-45 and 47-51 were previously withdrawn. Claim 55 has been amended. Claims 26, 31-32, 34, 36-41, 46, and 52-61 are in the case and are before the Examiner.

I. The Amendments

Claim 55 has been amended to add a period. The Examiner is thanked for noting the error.

This amendment adds no new matter.

II. The Action

A. Rejection Under 35 USC §102(b)

Withdrawal of the rejection of claims 26, 27, 36, 37, 38, 40, 41, 46, and 54-56 under Section 102(b) as being anticipated by the disclosures of Kurtz et al. US Patent No. 5,691,189, is noted with appreciation.

B. Rejections Under 35 USC §103

1. Prior Rejection

Withdrawal of the rejection of claims 26, 27, 36, 37, 38, 40, 41, 46 and 54-57 as obvious over the disclosures of Kurtz, as above, in view of Sunstrom et al., *J. Membrane Biol.* 1996 **150**:127-132, is also noted with appreciation.

2. Current Rejections

a. First Rejection

Claims 26, 31, 32, 36, 38, 41, 46, 53-55 and 58-61 were rejected as allegedly obvious from the combined teachings of Pumpens et al, *Intervirology*, 1995 **38**:63-74 (Pumpens) and Slepushkin et al., *Vaccine*, 1995 **13(15)**:1399-1402 (Slepushkin). Briefly, Pumpens teaches that HBcAg or HBc particles are good epitope carriers and can accommodate epitopic sequences at the N-, or C-terminus as well as within the sequence. Slepushkin is said to teach that the full length M2 protein is highly conserved and could function as a subunit vaccine to protect mice upon expression in a baculovirus membrane preparation to protect mice from challenge, but could not protect mice from challenge when expressed as part of a vaccinia recombinant.

The Action asserts that the Slepushkin disclosure at page 1402, col. 1, paragraph 1, provides the motivation for modifying its M2 with the HBc carrier of Pumpens, because that paper teaches that "others have failed to find any protective effect against challenge with influenza virus following vaccination of mice or ferrets with a vaccinia-M2 recombinant".

It is, however, submitted that that quoted statement of "motivation" of Slepushkin is inadequate. In particular, Slepushkin did demonstrate protection from influenza by his M2 composition, thereby overcoming the problems of the prior art to which he refers. Consequently, there existed no apparent motivation to *further* modify the M2 composition of Slepushkin.

A key distinction between the combination of Pumpens and Slepushkin and the claimed invention is that the proposed combination would suggest the use of the full-length M2 (as did Slepushkin, see page 1399, col. 2, paragraph 2), whereas the claimed construct employs an *extracellular* part of M2 (*i.e.*, "M2e"). The total length of M2 is 97 residues, whereas the maximal length of M2e is 23 or 24 of those residues, with shorter sequences also being useful. There is, however, no teaching from either relied-on paper that suggests that one should use anything except the longer, full length sequence.

In particular, Slepushkin reports that treatment of mice with a membrane preparation enriched with *full-length* M2 enhances clearance of influenza virus from the lungs of such mice and protects them from lethal challenge with influenza. Hence, the favourable effects of Slepushkin are achieved using *full-length* M2, and nothing in Slepushkin suggests that those effects were due to or could (also) be obtained using M2e, the *extracellular* portion of M2.

Thus, Slepushkin shows in Table 2 that high titre serum antibodies were obtained against epitope(s) *in both* the extracellular (peptide #1) and intracellular (peptides #7 and #8) domains of M2. Slepushkin does not contemplate which of

these serum antibodies, if a single group at all, contribute to the immune protection observed in the animals vaccinated with full-length M2. On the contrary, Slepushkin states: "this effect could *not* be attributed exclusively to antibody to any or all of the antigenic sites… of M2" (Slepushkin: page 1402, col. 1, lines 4-9).

In fact, Slepushkin failed to provide any indication for the role of these serum antibodies in immunoprotection by passive transfer of the sera *in vitro* and, above all, *in vivo*. For example, Slepushkin remarks: "we have been unable to show that serum from M2-vaccinated mice can limit virus infectivity *in vitro* or transfer immunity *in vivo*" (Slepushkin: page 1402, col. 1, l. 9-12).

In view of the lack of specificity concerning the relevance of the different portions of M2 for the effects seen in Slepushkin, the latter can at most suggest immunogenic compositions comprising full-length M2. Those disclosures neither teach nor suggest immunogenic compositions based on the extracellular portion of M2, as claimed in the present application.

It is further submitted that there is no basis for a skilled worker to change from using a vaccinia carrier system to a HBc carrier system for the synthetic vaccine because so much more work has been done using vaccinia in such vaccines than HBc. Thus, the undersigned carried out a search using the Google® search engine using the queries: for "vaccinia recombinant vaccine" and "HB core recombinant vaccine" and got 964,000 and 516,000 hits, respectively. Copies of the first

pages of those search results are attached as Exhibits A and B, respectively. Thus, there were almost twice as many articles published regarding use of vaccinia than use HBc as a synthetic vaccine. The skilled worker would have no motivation to switch to HBc as carrier when the world was using vaccinia.

It is therefore submitted that this basis for rejection should be withdrawn.

b. Second Rejection

Claim 37, "wherein the fusion product [of the immunogenic composition of claim 26] is anchored in the membrane of an acceptor cell expressing the fusion product" has been rejected over the combined teachings of Pumpens and Slepushkin as above further in view of Highfield et al., AU-B-49273/90. The Highfield disclosure is used to support the assertion that a skilled worker could express "a fusion construct from any acceptable cell line." This basis for rejection cannot be agreed with for several reasons and is respectfully traversed.

First, as noted above, the combination of Pumpens and Slepushkin does not lead one of ordinary skill to the subject matter of claim 26 and therefore the addition of the Highfield disclosures that add nothing regarding the deficiencies of those teachings cannot make dependent claim 37 obvious. Thus, this basis for rejection should be withdrawn.

Second, even if the combination of the Pumpens and Slepushkin teachings were to lead a skilled worker to the subject matter of claim 26, and even if Highfield teaches that a skilled worker could express "a fusion construct from any

acceptable cell line", neither of which is believed to be the case, it is submitted that a teaching of expression in "any acceptable cell line" is quite different from expression that leads to "the fusion product [of claim 26 being] anchored in the membrane of an acceptor cell expressing the fusion product" as is claimed.

The asserted basis assumes that every protein that is expressed in "any acceptable cell line" is automatically transported to and anchored in the cell membrane. There is no evidence for either phenomenon in the record, let alone both phenomena. As such, this basis for rejection should be withdrawn.

c. Third Rejection

Claims 34 and 39 were rejected as allegedly obvious from the combined teachings of Pumpens and Slepushkin as in the first rejection and Highfield in the second rejection further in view of van de Guchte et al., *Appl. Environm. Microbiol.* 1989 **55(1):**224-228 (van de Guchte). The van de Guchte disclosure teaches lactococcal expression vectors that can express a wide range of heterologous genes. This basis for rejection cannot be agreed with and is respectfully traversed.

Claims 34 and 39 respectively recite that the immunogenic composition of claim 26 "comprises Lactococci cells expressing said fusion product in or on their cell membrane, and said cells optionally release said fusion product", and that the influenza immunogenic composition of claim 26 comprises Lactococci cells expressing the fusion product in or on their

cell wall". As has already been pointed out, the combination of teachings of Pumpens and Slepushkin does not lead a skilled worker to the subject matter of claim 26. In addition, the teachings of Highfield add nothing of value toward getting to the subject matter claimed in claim 37. For those same reasons, it is submitted that the addition of teachings of van de Guchte cannot make that which is not obvious by simply using what may be a well-known expression system.

It is submitted that there is no expectation of success in regard to the recited and above quoted subject matter regarding expression of the immunogenic materials in or on the Lactococci cell walls. It is thus submitted that this basis for rejection should also be withdrawn

d. Fourth Rejection

Claims 40 and 53 that depend from claim 26 have been rejected over the combined teachings of Pumpens and Slepushkin as discussed above, further in view of Kedar et al., US Patent No. 5,919,480 (Kedar). The Kedar patent is said to disclose the influenza hemagglutinin and neuraminidase proteins in combination with a cytokine as a vaccine. The Action asserts that it would be obvious to add known vaccine antigens and an immunostimulating cytokine in influenza immunogenic composition of claim 26.

The Action admits that Pumpens and Slepushkin are silent on the incorporation of other influenza antigens or cytokines. Although the Action does not so state, the Kedar teaching is silent on 1) the use of any part of the M2 protein

as an immunogen, 2) the use of a fusion protein, and 3) on the use of HBc as a carrier protein. This basis for rejection cannot be agreed with and is respectfully traversed.

The previously-made arguments concerning the inapplicability of the combination of the Pumpens and Slepushkin teachings to suggestion of the immunogenic composition of claim 26 are hereby repeated here. It is apparent that with no mention being made of HBc, a fusion protein or the M2 protein, the Kedar patent has no disclosures that could overcome the deficits already noted in the Pumpens and Slepushkin teachings regarding the claimed subject matter. Inasmuch as the subject matter claimed in claims 40 and 52 is dependent upon claim 26, because that independent claim is not obvious from the basic Pumpens and Slepushkin teachings, the dependent claim cannot be obvious from a teaching that does not augment the first two disclosures. This basis for rejection s should therefore be withdrawn.

e. Fifth Rejection

Claims 26, 31, 32, 36, 38, 41, 46, 53, 54, and 57-61 were rejected as allegedly obvious from the teachings of Pumpens and Slepushkin as discussed before further in view of Sunstrom et al., *J. Membrane Biol.*, 1996 **150**:127-132 (Sundstrom) or Hongo et al., *J. Virol.*, April 1997 **71(4)**:2786-2792 (Hongo). The Sunstrom teaching is cited for its disclosure that influenza B NB protein forms an ion channel, whereas Hongo is said to teach that influenza C virus CM2 protein has similar properties to the M2 protein. The Action's logic is that because the NB and CM2

proteins are similar in function to M2, it would be obvious to use either or both in place of M2 in a Pumpens construct. This basis for rejection cannot be agreed with and is respectfully traversed.

First, the previous discussion of the inadequacies of the combination of Pumpens and Slepushkin are repeated here by reference. As such alone, this basis for rejection should be withdrawn.

In addition, attached Exhibit C is a copy of an abstract of the paper Sansom et al., *PEDS*, 1993 6(1):65-74 in which the structure of the influenza M2 ion channel is described. The Abstract is noted on enclosed Form PTO/SB/08B. As will be seen, the Abstract states:

> a bundle of four parallel M_2 transbilayer helices surrounds a central ion-permeable pore. Analysis of helix amphipathicity was used to aid determination of the orientation of the helices about their long axes. The helices are tilted such that the N-terminal mouth of the pore is wider than the C-terminal mouth. The channel is lined by residues V27, S31 and I42. Residues D24 and D44 are located at opposite mouths of the pore, which is narrowest in the vicinity of I42.

As noted before, the claims recite an "antigen that is an immunogenic extracellular part of . . ." one of three influenza-related proteins, of which the M2 of influenza A is illustrative. That extracellular part of the M2 protein can contain up to 24 residues, with Fig. 1C of the present application identifying one embodiment that including residues 2-24 from the N-terminus of the protein.

The above quote from the enclosed Sansom paper Abstract indicates that M2 residue 24 is at one mouth of the ion channel with residue 44 being at the other mouth. That means that the channel lies there between and is made from residues 25-43. That being the case, disclosures such as those relied on here from Slepushkin, Sundstrom and Hongo that teach use of whole proteins or the ion channel-forming portions of the proteins are inapposite to the claims, as those portions of the respective proteins are not part of the "immunogenic extracellular part of . . ." one of those three recited proteins, but are part of the transmembrane portions that are not claimed. It is thus submitted that this basis for rejection should be withdrawn as it is clearly drawn to subject matter other than that which is claimed.

III. Summary

Claim 55 has been amended. Each basis for rejection or objection has been overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution. It is noted that the undersigned

is a new counsel for this application. A formal Power of Attorney is enclosed herewith.

Respectfully submitted,

By _____
Edward P. Gamson Reg. No. 29,381

WELSH & KATZ, LTD.
120 South Riverside Plaza, 22nd Floor
Chicago, Illinois 60606
Phone (312) 655-1500
Fax No. (312) 655-1501

Enclosures
- Petition for Extension of Time and fee
- Form PTO/SB/08B
- Exhibits A & B (Search Results)
- Exhibit C (Abstract)